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ABSTRACT

Aims/hypothesis: It has been suggested that air pollution may increase the risk of type 2 diabetes but data on particulate matter with diameter <2.5 μm ($PM_{2.5}$) are inconsistent. We examined the association between long-term exposure to $PM_{2.5}$ and diabetes incidence.
Methods: We used the Danish Nurse Cohort with 28,731 female nurses who at recruitment in 1993 or 1999 reported information on diabetes prevalence and risk factors, and obtained data on incidence of diabetes from National Diabetes Register until 2013. We estimated annual mean concentrations of $PM_{2.5}$, particulate matter with diameter <10 μm (PM_{10}), nitrogen oxides (NO_x) and nitrogen dioxide (NO_2) at their residence since 1990 using a dispersion model and examined the association between the 5-year running mean of pollutants and diabetes incidence using a time-varying Cox regression.
Results: Of 24,174 nurses 1137 (4.7%) developed diabetes. We detected a significant positive association between $PM_{2.5}$ and diabetes incidence (hazard ratio; 95% confidence interval: 1.11; 1.02–1.22 per interquartile range of 3.1 μg/m^3), and weaker associations for PM_{10} (1.06; 0.98–1.14 per 2.8 μg/m^3), NO_2 (1.05; 0.99–1.12 per 7.5 μg/m^3), and NO_x (1.01; 0.98–1.05 per 10.2 μg/m^3) in fully adjusted models. Associations with $PM_{2.5}$ persisted in two-pollutant models. Associations with $PM_{2.5}$ were significantly enhanced in never smokers (1.24; 1.09–1.42), and augmented in obese (1.25; 1.06–1.47) and subjects with myocardial infarction (1.32; 0.86–2.02), but without significant interaction.
Conclusions/interpretation: Fine particulate matter may the most relevant pollutant for diabetes development among women, and non-smokers, obese women, and heart disease patients may be most susceptible.

1. Introduction

Air pollution is among the leading causes of morbidity and mortality worldwide, accounting for 4.5% of the Global Disability Adjusted Life Year in 2010 (Lim et al., 2012). The global type 2 diabetes epidemic is a major public health challenge worldwide, and one of the greatest contributors to the global burden of disease, with an estimated 65% increase in diabetics by 2025, to 380 millions (World Health Organization. Global Status Report on Noncommunicable Diseases, 2014). Experimental studies have provided biological plausibility for a link between air pollution and type 2 diabetes risk by showing how exposure to particulate matter with diameter <2.5 μm ($PM_{2.5}$) among obese mice provoked insulin resistance and adiposity, with systemic inflammation as the key mechanism (Sun et al., 2009). This has led to a rise in epidemiological studies of long-term exposure to air pollution and type 2 diabetes, and several recent meta-analyses conclude that air pollution is likely a risk factor (Balti et al., 2014; Eze et al., 2015; Wang et al., 2014; Esposito et al., 2015; Thiering & Heinrich, 2015). However, the results from epidemiological studies are not fully consistent, with a study published after meta-analyses (Balti et al., 2014; Eze et al., 2015; Wang et al.,

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2014; Esposito et al., 2015; Thiering & Heinrich, 2015), failing to detect an association between $PM_{2.5}$ and diabetes incidence (Park et al., 2015). Of the twelve epidemiological studies on long-term exposure to air pollution and diabetes, five studied prevalence (Brook et al., 2008; Pearson et al., 2010; Dijkema et al., 2011; Eze et al., 2014; To et al., 2015), six incidence (Krämer et al., 2012; Puett et al., 2011; Andersen et al., 2012; Coogan et al., 2012; Chen et al., 2013; Weinmayr et al., 2015), and one both (Park et al., 2015). Two studies on diabetes prevalence and NO_2 found no associations (Brook et al., 2008; Pearson et al., 2010; Dijkema et al., 2011), while four detected associations with at least one pollutant studied: particulate matter with diameter <10 μm (PM_{10}) (Eze et al., 2014), $PM_{2.5}$ (Park et al., 2015; Pearson et al., 2010; To et al., 2015), nitrogen dioxide (NO_2)[13] or nitrogen oxides (NO_x)[9]. Of the seven cohort studies, six (Krämer et al., 2012; Andersen et al., 2012; Coogan et al., 2012; Chen et al., 2013; Weinmayr et al., 2015) detected associations between diabetes incidence and at least one pollutant in the study: two with PM_{10} (Krämer et al., 2012; Weinmayr et al., 2015), two with NO_2 (Krämer et al., 2012; Andersen et al., 2012), one with $PM_{2.5}$ (Chen et al., 2013), and one with NO_x (Coogan et al., 2012). However, US studies with data from three large cohorts, American Nurse Health Study (Puett et al., 2011), Health Professionals Study (Puett et al., 2011), and Multi Ethnic Study of Atherosclerosis (MESA) (Park et al., 2015) all failed to detect significant associations between diabetes incidence and air pollution, specifically $PM_{2.5}$ (Park et al., 2015; Puett et al., 2011), PM_{10} (Puett et al., 2011), and NO_x (Park et al., 2015). Furthermore, five studies with data on $PM_{2.5}$ (Park et al., 2015; Puett et al., 2011; Coogan et al., 2012; Chen et al., 2013; Weinmayr et al., 2015) and diabetes incidence report mixed results, with only one, by Chen et al. (2013), detecting significant positive associations (hazard ratio (HR); 95% confidence interval (CI): 1.11; 1.02–1.21 per 10 $\mu g/m^3$), while Park et al. (2015) (1.02; 0.95–1.10 per 2.4 $\mu g/m^3$), Puett et al. (2011) (1.03; 0.96–1.10 per 4 $\mu g/m^3$), and Weinmayr et al. (2015) (1.08; 0.89–1.29 per 2.3 $\mu g/m^3$) did not detect significant associations, and Coogan et al. (2012) detected strong positive, but non-significant association (1.63; 0.78–3.44 per 10 $\mu g/m^3$). Finally, it is uncertain which pollutant is most relevant for diabetes development, as few cohorts have data on multiple pollutants (Krämer et al., 2012; Puett et al., 2011; Coogan et al., 2012; Weinmayr et al., 2015) and only two present two-pollutant models, both showing weak associations with $PM_{2.5}$ (Puett et al., 2011; Coogan et al., 2012). Coogan et al. (Coogan et al., 2012) reported stronger association with NO_x than with $PM_{2.5}$, while Puett et al. (Puett et al., 2011) found stronger effects with coarse particles $PM_{2.5-10}$ than with $PM_{2.5}$, contrary to the evidence from experimental studies in mice (Sun et al., 2009) which found $PM_{2.5}$ to contribute to the development of diabetes.

Here we examined the association between long-term exposure to $PM_{2.5}$, PM_{10}, NO_2 and NO_x, estimated at the residence by a high-resolution dispersion model, and incidence of diabetes in Danish female nurses aged over 44 years, in single and two-pollutant models, and tested for effect modification by relevant lifestyle, co-morbidities, and level of urbanization.

2. Methods

2.1. The Danish Nurse Cohort

The Danish Nurse Cohort (Hundrup et al., 2012) was inspired by the American Nurses' Health Study to initially investigate the health effects of hormone replacement therapy (HRT) in a European population. The cohort was initiated in 1993 by sending a questionnaire to 23,170 female members of the Danish Nursing Organization who were older than 44 years at the time. The Danish Nursing Organization includes 95% of all nurses in Denmark. In total, 19,898 (86%) nurses replied, and the cohort was reinvestigated in 1999 when additionally 10,534 nurses (who had had reached the age of 44 years in the period 1993–99) were included, and in 2009, but without inclusion of new nurses. The questionnaire included questions on socio-economic and working conditions, parents' occupation, weight and height including birth-weight, lifestyle (diet, smoking, alcohol consumption and leisure time physical activity), self-reported health, family history of cardiovascular disease and cancer, parity, age at first birth, age of menarche and menopause, use of oral contraceptives and hormone therapy (HT), removal of uterus and ovaries. In this study we used the earliest baseline information from 1993 (19,898) or 1999 (8833) for 28,731 female nurses.

The cohort was linked to the Central Population Register (Pedersen, 2011) to obtain the nurses' residential address information since 1971 until 2013, and vital status information at 31st December 2013 (active, date of death or emigration), and to the Danish Address Database to obtain the geographical coordinates.

2.2. Danish National Diabetes Register

The Danish National Diabetes Register (NDR) (Carstensen et al., 2011) was established to describe and monitor the prevalence and incidence of diabetes in Denmark since 1995, by linking four existing Danish registries: the National Patient Register (NPR) (Lynge et al., 2011), containing hospital discharge diagnosis since 1973, the National Health Service Register (NHSR) (Andersen et al., 2011), with information on all services provided by general and specialist practitioners since 1990, and the Danish National Prescription Registry (DNPR) (Kildemoes et al., 2011), containing all prescriptions dispensed at Danish pharmacies since 1993. NDR classifies people as diabetic if they fulfill a minimum of one of the following criteria: 1) diabetes hospital discharge diagnosis since 1995 (ICD-10 code E10-14, DH36.0, DO24) in the NPR; 2) chiropody as a diabetic patient, 3) five blood-glucose measures within one year, or 4) two blood glucose measures per year in five coherent years in the NHSR; or 5) second purchase of insulin or oral anti-diabetic drugs within 6 months registered in DNPR (Carstensen et al., 2011). Date of the first fulfilled criterion is considered the date of the onset of diabetes, and the majority of diabetic have several criteria fulfilled. Since the results of blood glucose measurements (criteria 3 and 4) are not available in the NHSR, the nurses who had either criteria 3 or 4 as the single inclusion criteria in NDR were not considered diabetic in this study. NDR does not distinguish between type 1, type 2 or gestational diabetes. Because of the different dates of initiation of the underlying registers and accumulation of prevalent cases, only incidence information after 1st January 1995 is reliable (Carstensen et al., 2011). Thus, the incidence of diabetes in this study was defined as the earliest record in the NDR occurring between 1st January 1995 and 31st December 2012.

2.3. Air pollution exposure data

We used the newly updated, high-resolution Danish air pollution dispersion modeling system (AirGIS) to estimate exposure to outdoor air pollution (Jensen et al., 2001) (more detail in the ESM). The necessary input data for carrying out the exposure modeling has been established for the first time in Denmark for particulate matter ($PM_{2.5}$ and PM_{10}) starting in 1990, whereas for the gaseous nitrogen oxide pollutants (NO_2 and NO_x) input data have been established since 1971. Since focus of this paper is $PM_{2.5}$, we have calculated annual mean concentrations of $PM_{2.5}$, PM_{10}, NO_2, and NO_x since 1990 at the residential addresses for nurses who had complete information on residential address history for at least 80% of the time since 1990 until 2013. Five-year running mean of available annual concentrations of $PM_{2.5}$, PM_{10}, NO_2, and NO_x was the main exposure proxy, as this was the longest possible exposure window between 1990, when modeling of $PM_{2.5}$ begun, and the beginning of the study follow-up in 1995. Additionally, 24-year running mean of NO_2 and NO_x, as the longest possible exposure window, was used in sensitivity analyses.

2.4. Statistical analysis

We applied the extended Cox proportional hazards regression model to test the incidence of diabetes as a function of air pollution exposure, with age as the underlying time scale. Start of follow-up was at the age on the date of recruitment (1st April 1993 or 1st April 1999) or start of registration of diabetes (1st January 1995), whichever came latest, and end of follow-up was age at the date of diabetes onset, date of death, emigration or 31st of December 2012, whichever came first. The effect of air pollutants was evaluated in single- and two-pollutant models in several steps: Model 1) crude model, adjusted only for age; Model 2) main, fully adjusted model, additionally adjusted for smoking status (never, current, previous), smoking intensity (g/day), alcohol consumption (g/week), physical activity (low, medium, high), body mass index (BMI) (underweight, normal, overweight, obese), the consumption of fatty meat (yes, no), the consumption of fruit and vegetables (yes, no), employment status (employed, unemployed, retired, homeward, other), and marital status (married, separated, divorced, unmarried, widow), myocardial infarction (MI) and hypertension; and model 3) additionally adjusted for average income at municipality, as a proxy of neighborhood-level socio-economic status. Nurses have answered how many cigarettes, cheroots, cigars, and pipes they smoked daily, and smoking intensity was calculated by equating a cigarette to 1 g, a cheroot or a pipe to 3 g, and a cigar to 4.5 g of tobacco. The model was stratified by year of birth to take into account the effect of calendar time. We modeled the air pollution exposure assuming linear and time dependent effect by applying a 5-year moving time window for all pollutants that calculated the average pollution over a given time interval prior to the current time period, and 24-year mean, as a sensitivity analyses. Only observations where air pollution information was known in at least 80% of the time up to a given time period, was included in the analysis. Potential effect modification of association between air pollutant and diabetes incidence by age, physical activity, BMI, smoking status, MI, hypertension, and level of urbanization was examined by including interaction terms in the model and tested by the likelihood ratio test. Finally, two-pollutant models were performed for pairs of pollutants: $PM_{2.5}$ and NO_2, NO_2 and PM_{10}. NO_x was not included in the two-pollutant model since NO_2 and NO_x were highly correlated (correlation coefficient $r = 0.92$). Similarly, $PM_{2.5}$ and PM_{10} were not modeled together due to high correlation ($r = 0.77$) (Table A, ESM). This is expected since NO_2 is part of NO_x (NO_x is the sum of nitrogen monoxide (NO) and NO_2), and $PM_{2.5}$ is part of PM_{10}. All effects are reported by hazard ratios (HRs) and 95% confidence intervals (CIs), per interquartile range (IQR) increase in 5-year mean of pollutant levels ($PM_{2.5}$: 3.14 μg/m^3, PM_{10}: 2.79 μg/m^3, NO_2: 7.53 μg/m^3, NO_x: 10.19 μg/m^3), to facilitate direct comparison between the pollutants. The graphical presentation of a functional form of an association between $PM_{2.5}$ and diabetes was produced using restricted cubic spline in the design library, and linearity assumption tested using log-likelihood test. Since hypertension, MI, and BMI are risk factors for diabetes, but also associated with air pollution, and thus possible mediators of an association between air pollution and diabetes, we have performed sensitivity analyses fitting model 2 without these three variables. All analysis and graphical presentations were performed using the statistical software R 3.2.0.

3. Results

Of the total 28,731 nurses in the DNC, we excluded 192 who died or emigrated between cohort entry on 1st April 1993 and start of follow-up at 1st January 1995 (start of NDR), 588 who had reported having diabetes via questionnaire at the cohort baseline, and additional 31 who did not report having diabetes, but were found to have diabetes registered in NDR before baseline. We additionally excluded 2418 nurses with missing information on covariates and 1328 due to missing address information or inability to geocode address, leaving 24,174 nurses for the final analyses.

Mean follow-up was 15.3 years giving total of 370,367 person-years of observations, during which 1137 nurses developed diabetes, with incidence rate of 3 new cases per 1000 person-years.

Mean age at baseline was 54 years with between 44 and 95 years (Table 1). The nurses who developed diabetes had higher BMI, smoked more, consumed less alcohol, had lower physical activity level,

Table 1
Characteristics of the Danish Nurse Cohort ($n = 24.174$) at baseline by incident diabetes status at follow-up.

Baseline characteristics	Total $n = 24.174$	Diabetes $n = 1137$	Non diabetic $n = 23.037$
Age, mean (SD)	54.0 (8.2)	56.5 (8.1)	53.9 (8.2)
BMI, mean (SD)	23.6 (3.4)	26.4 (4.4)	23.5 (3.3)
Underweight (BMI < 18.5 kg/m^2), n (%)	580 (2.4)	13 (1.1)	567 (2.5)
Normal (BMI 18.5–25 kg/m^2), n (%)	16,960 (70.2)	470 (41.3)	16,490 (71.6)
Overweight (BMI 25–30 kg/m^2), n (%)	5374 (22.2)	433 (38.1)	4941 (21.4)
Obese (BMI > 30 kg/m^2), n (%)	1260 (5.2)	221 (19.4)	1039 (4.5)
Never smoked, n (%)	8372 (34.6)	358 (31.5)	8014 (34.8)
Current smoker, n (%)	8441 (34.9)	455 (40.0)	7986 (34.7)
Previously smoked, n (%)	7361 (30.5)	324 (28.5)	7037 (30.5)
Smoking intensity[a] (g/day), mean (SD)	7.9 (9.2)	9.6 (10.6)	7.8 (9.1)
Never consumed alcohol, n (%)	3668 (15.2)	248 (21.8)	3420 (14.8)
Alcohol consumption[b] (g/week), mean (SD)	115.3 (127.4)	108.5 (137.2)	115.6 (126.9)
Low physical activity, n (%)	1539 (6.4)	123 (10.8)	1416 (6.1)
Medium physical activity, n (%)	16,099 (66.6)	783 (68.9)	15,316 (66.5)
High physical activity, n (%)	6536 (27.0)	231 (20.3)	6305 (27.4)
Regularly eat fruit and vegetables, n (%)	23,568 (97.5)	1103 (97)	22,465 (97.5)
Consume fatty meat, n (%)	2301 (9.5)	151 (13.3)	2150 (9.3)
Hypertension, n (%)	2827 (11.7)	313 (27.5)	2514 (10.9)
MI, n (%)	166 (0.7)	19 (1.7)	147 (0.6)
Urban Area, n (%)	3628 (15.0)	197 (17.3)	3431 (14.9)
Rural, n (%)	10,014 (41.4)	446 (39.2)	9568 (41.5)
Provincial, n (%)	10,532 (43.6)	494 (43.4)	10,038 (43.6)
Married, n (%)	17,114 (70.8)	746 (65.6)	16,368 (71.1)
Separated, n (%)	414 (1.7)	20 (1.8)	394 (1.7)
Divorced, n (%)	2773 (11.5)	153 (13.5)	2620 (11.4)
Single, n (%)	2354 (9.7)	129 (11.3)	2225 (9.7)
Widow, n (%)	1519 (6.3)	89 (7.8)	1430 (6.2)
Employed, n (%)	19,263 (79.7)	812 (71.4)	18,451 (80.1)
Homemaker and others, n (%)	732 (3.0)	27 (2.4)	705 (3.1)
Retired, n (%)	4092 (16.9)	290 (25.5)	3802 (16.5)
Unemployed, n (%)	87 (0.4)	8 (0.7)	79 (0.3)
Municipality income (DKK)[c], mean (SD)	164,376 (24,678)	164,282 (24,680)	164,381 (24,678)
Annual air pollution at baseline address			
$PM_{2.5}$ (μg/m^3), mean (SD)	18.1 (2.8)	18.7 (2.8)	18.1 (2.8)
PM_{10} (μg/m^3), mean (SD)	21.7 (2.9)	22.3 (2.9)	21.7 (2.9)
NO_2 (μg/m^3), mean (SD)	12.5 (7.9)	13.4 (8.7)	12.5 (7.9)
NO_x (μg/m^3), mean (SD)	18.4 (22.7)	19.9 (23.2)	18.3 (22.6)

SD: Standard deviation, BMI: body mass index, MI: myocardial infarction. DKK: Danish crown.
[a] Among ever smokers.
[b] Among alcohol consumers.
[c] Average income at the municipality at cohort baseline (1993 or 1999).

consumed more fatty meat and less fruit and vegetables, and had higher rate of hypertension and MI at baseline than nurses who did not develop diabetes.

Nurses from Danish Nurse Cohort resided all around Denmark with wide geographical variation (Fig. 1), with 15% residing in urban areas (population density ≥ 5220 persons/km^2), 43.6% in provincial towns (180–5220 persons/km^2) and 41.4% in rural areas (<180 persons/km^2) at the cohort baseline, which corresponds closely to distribution of Danish population. The estimated air pollution levels at baseline varied greatly (Fig. 1, Fig. A—ESM). Levels of NO_2 and NO_x, proxy of road traffic pollution, were high in urban areas, provincial and small towns (Fig. 1). Levels of $PM_{2.5}$ and PM_{10} were also high in urban areas (traffic), as well as in the South Eastern Denmark due to long-range transported secondary pollution. Furthermore, levels of PM_{10} were high on the West Coast indicating strong influence of sea spray. Average air pollution levels for all pollutants were steadily decreasing during study period (Fig. B—ESM). Nurses who developed diabetes had higher levels of all pollutants at cohort baseline residence than those who did not develop diabetes (Table 1).

We found a statistically significant positive association between exposure to $PM_{2.5}$ and diabetes incidence with HR of 1.14 (1.04–1.24) per IQR of 3.1 μg/m^3 increase in 5-year mean exposure in a crude model (Table 2). HR slightly attenuated in the fully adjusted model to 1.11 (1.02–1.22), which remained unchanged in the sensitivity model models without hypertension, MI, or BMI, potential mediating variables. This corresponds to 41% increase in diabetes risk (1.05–1.88) per 10 μg/m^3 increase in $PM_{2.5}$ levels. We did not detect significant deviation from linearity, supporting linear dose-response relationship between exposure to $PM_{2.5}$ and diabetes incidence, notably with leveling off and wide confidence intervals in exposure range above 20 μg/m^3 (Fig. 2).

Table 2
Association between air pollution (5-year running mean) and diabetes incidence (n = 1.137) among 24,174 Danish Nurse Cohort participants.

Pollutant	Unit (μg/m^3)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)
$PM_{2.5}$	3.1	1.14 (1.04–1.24)	1.11 (1.02–1.22)	1.11 (1.01–1.22)
PM_{10}	2.8	1.08 (1.00–1.16)	1.06 (0.98–1.14)	1.06 (0.98–1.14)
NO_2	7.5	1.06 (1.00–1.12)	1.05 (0.99–1.12)	1.05 (0.98–1.12)
NO_x	10.2	1.02 (0.99–1.05)	1.01 (0.98–1.05)	1.01 (0.98–1.05)
$PM_{2.5}$	10	1.50 (1.13–2.00)	1.41 (1.05–1.88)	1.39 (1.04–1.86)
PM_{10}	10	1.32 (1.02–1.72)	1.22 (0.93–1.59)	1.24 (0.95–1.62)

HR: hazard ratio; CI: confidence intervals.
[a] Adjusted for age.
[b] Adjusted for age, calendar time, smoking (status, intensity), physical activity, alcohol consumption, fatty meat consumption, fruit and vegetable consumption, employment status, marital status, BMI (body mass index), hypertension and MI (myocardial infarction).
[c] Included covariates in Model 2[b] + average income at the municipality at baseline.

We found weak, positive, and statistically insignificant associations between diabetes incidence and exposure to PM_{10} (1.06; 0.98–1.14) per IQR of 2.8 μg/m^3, NO_2 with HR of 1.05 (0.99–1.12) per IQR of 7.5 μg/m^3, and NO_x (1.01; 0.98–1.05) per IQR of 10.2 μg/m^3 in the fully adjusted model. We found similar association with NO_2 (1.06; 0.98–1.14) and NO_x (1.01; 0.97–1.05) per IQR increase in 24-year mean (sensitivity analyses, results not show). The observed association between long-term exposure to $PM_{2.5}$ and diabetes incidence remained robust

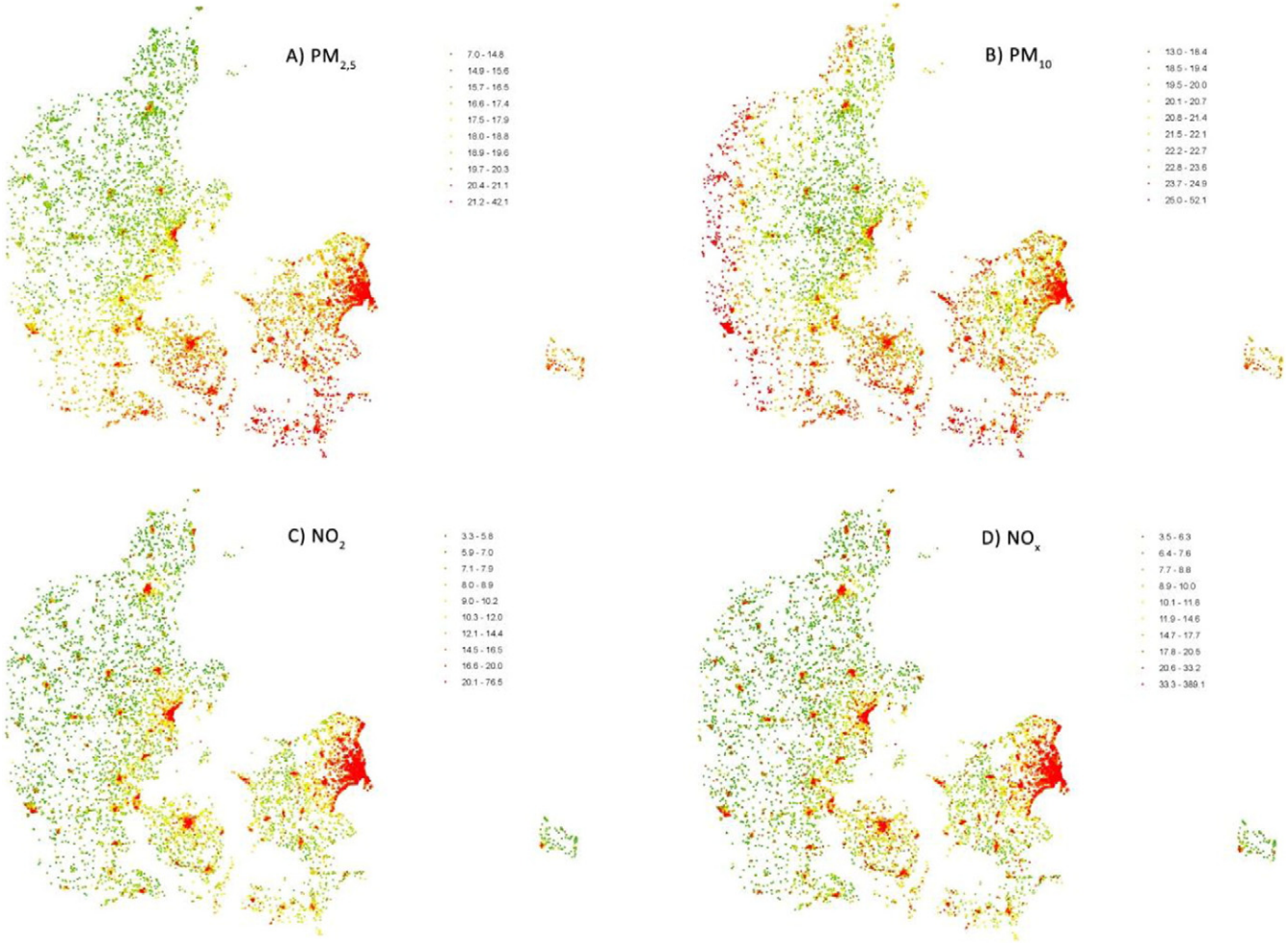

Fig. 1. Levels of $PM_{2.5}$, PM_{10}, NO_2 and NO_x (mean annual level) at the residence of 24,174 nurses from Danish Nurse Cohort at baseline in 1993 or 1999.

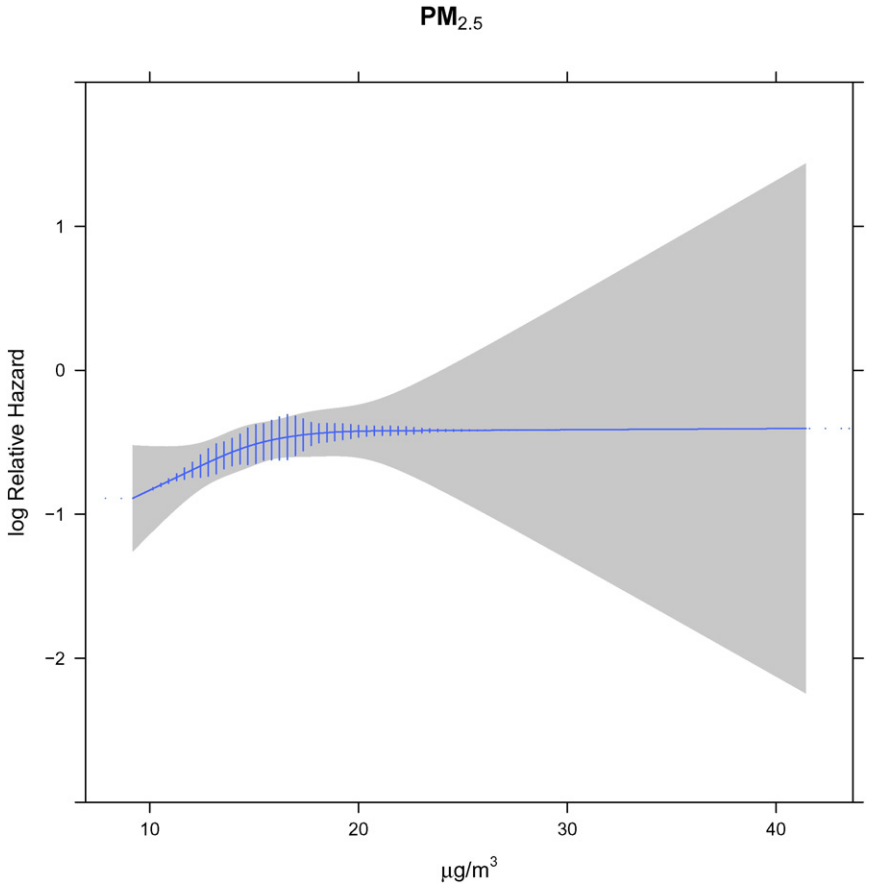

Fig. 2. Association between exposure to $PM_{2.5}$ (5-year running mean) levels at residence and incident diabetes ($n = 1.137$) (log relative hazard with 95% CI) for 24,174 nurses from Danish Nurse Cohort, adjusted for age, calendar time, smoking status, smoking intensity, physical activity, alcohol consumption, fatty meat consumption, fruit and vegetables consumption, hypertension, myocardial infarction, employment status, marital status and body mass index.

(1.11; 1.02–1.22) in two-pollutant model with NO_2 (0.99; 0.90–1.08) (Table 3), while associations with NO_2 attenuated.

We found that smoking status was a statistically significant modifier (p value for interaction 0.01), of association between $PM_{2.5}$ and diabetes, with effect of air pollution limited to never (1.24; 1.09–42) and previous smokers (1.19; 1.03–1.36) (Table 4). Obese women (BMI > 30 kg/m^2) had enhanced risk of diabetes related to exposure to $PM_{2.5}$ (1.25; 1.06–1.47), although without significant interaction with BMI ($p = 0.37$) (Table 4). Highest risk of diabetes related to $PM_{2.5}$ was observed in nurses with MI before diabetes onset (1.32; 0.86–2.02), but based on few cases, interaction with MI did not reach statistical significance ($p = 0.43$). There were no significant modifications of an association between long-term exposure to $PM_{2.5}$ and diabetes incidence by age, physical activity, BMI, MI, hypertension, or level of urbanization.

4. Discussion

We found that long-term exposure to $PM_{2.5}$ was associated with increased risk of diabetes. The risk was limited to never and previous smokers, and was enhanced in obese and women with cardiovascular disease.

Our results are consistent to those by Chen et al. (Chen et al., 2013) who found 11% (1.02–1.21) increase in diabetes risk in 62,012 men and women from Ontario, Canada, and enhanced effects in women of 17% (1.03–1.32) for each 10 µg/m^3 increase in $PM_{2.5}$. This estimate is considerably lower than our estimate of 41% (1.05–1.88) increase per 10 µg/m^3 increase in $PM_{2.5}$. $PM_{2.5}$ levels in the Canadian study were lower (10.6 µg/m^3) (Chen et al., 2013) than in our (18.1 µg/m^3). Coogan et al. (2012) has in 3992 African American women from Los Angeles,

Table 3
Association[a] between air pollution (5-year running mean) and diabetes incidence ($n = 1.137$) among 24,174 Danish Nurse Cohort participants in one and two-pollutant models.

Pollutant	IQR (µg/m^3)	One pollutant models	Two-pollutant models	
		HR (95% CI)	HR (95% CI)[b]	HR (95% CI)[c]
$PM_{2.5}$	3.1	1.11(1.02–1.22)	1.13 (0.99–1.29)	–
NO_2[c]	7.5	1.05(0.99–1.12)	0.99 (0.90–1.08)	1.03 (0.95–1.12)
PM_{10}	2.8	1.06(0.98–1.14)	–	1.03 (0.94–1.13)

HR: hazard ratio; CI: confidence intervals.
[a] Adjusted for age, calendar time, smoking (status, intensity), physical activity, alcohol consumption, fatty meat consumption, fruit and vegetables consumption, hypertension, MI (myocardial infarction), employment status, marital status and BMI (body mass index).
[b] NO_2 & PM_{10}.
[c] NO_2 & PM_{10}.

Table 4
Modification of association[a] between diabetes incidence ($n = 1.137$) and $PM_{2.5}$ (5-year running mean per interquartile range of 3.1 μg/m^3) by baseline characteristics and co-morbid conditions among 24,174 participants in the Danish Nurse Cohort.

Covariate		$N =$ 1137	IR	HR (95%CI)	p[b]
Age	<50	308	1.9	1.19 (1.00–1.42)	*0.49*
	50–60	456	3.3	1.04 (0.91–1.20)	
	>60	373	4.7	1.14 (0.98–1.32)	
Physical activity	Low	123	5.7	1.21 (0.98–1.49)	*0.71*
	Medium	783	3.1	1.10 (1.00–1.22)	
	High	231	2.2	1.10 (0.92–1.31)	
Smoking status	Never	358	2.7	1.24 (1.09–1.42)	*0.01*
	Previous	455	3.5	1.19 (1.03–1.36)	
	Current	324	2.8	0.97 (0.86–1.10)	
BMI	Underweight (<18.5 kg/m^2)	13	1.5	0.86 (0.43–1.75)	*0.37*
	Normal (18.5–25 kg/m^2)	470	1.7	1.08 (0.96–1.22)	
	Overweight (25–30 kg/m^2)	433	5.3	1.09 (0.96–1.24)	
	Obese (≥30 kg/m^2)	221	12.4	1.25 (1.06–1.47)	
MI	Yes	19	9.3	1.32 (0.86–2.02)	*0.43*
	No	1118	3.0	1.11 (1.01–1.21)	
Hypertension	Yes	313	7.5	1.15 (1.00–1.33)	*0.55*
	No	824	2.5	1.10 (0.99–1.21)	
Level of urbanization	Urban	197	3.5	1.10 (0.92–1.31)	*0.33*
	Rural	446	2.9	1.16 (1.01–1.33)	
	Provincial	494	3.0	1.02 (0.88–1.18)	

IR: incidence rate per 1000 person years; HR: hazard ratio; CI: confidence interval.
[a] Adjusted for age, calendar time, smoking (status, intensity), physical activity, alcohol consumption, fatty meat consumption, fruit and vegetables consumption, hypertension, MI (myocardial infarction), employment status, marital status and BMI (body mass index).
[b] From likelihood ratio test for interaction.

USA, with higher mean $PM_{2.5}$ levels (20.7 μg/m^3) than in our study, detected 63% (0.78–3.44) higher risk of diabetes per 10 μg/m^3 increase in $PM_{2.5}$, an estimate comparable to ours, but not reaching statistical significance (Coogan et al., 2012). Our results diverge from three cohort studies with data on $PM_{2.5}$ and diabetes incidence which found no associations (Park et al., 2015; Puett et al., 2011; Weinmayr et al., 2015). In 5839 USA adults from the MESA study, Park et al. (2015) failed to detect association with $PM_{2.5}$ (1.02; 0.95–1.10 per 2.4 μg/m^3), although slightly stronger effects in women (1.04; 0.94–1.16), in line with Chen et al. (2013), Park et al. (2015) utilized data from 6 US cities with mean $PM_{2.5}$ levels around 17 μg/m^3, similar to Danish levels. Similarly to Park et al., Puett et al. (2011) has in 74,412 nurses from American Nurse Health Study and 15,048 men from Health Professionals Study failed to link $PM_{2.5}$ to diabetes risk (1.03; 0.96–1.10 per 4 μg/m^3). Finally, Weinmayr et al. (2015) in 3607 individuals from the Recall Study in Germany with mean levels of $PM_{2.5}$ of 16.7 μg/m^3 found weak association with diabetes incidence (1.08; 0.89–1.29 per 2.3 μg/m^3), with weaker association in women.

The inconsistency in results from studies on $PM_{2.5}$ and diabetes incidence may be explained by differences in study populations, misclassification of exposure resulting from different modeling methods, or differences in the sources and toxicological composition of the $PM_{2.5}$ at the different locations. We benefited from high-resolution dispersion model providing historical annual mean (1990–2013) estimates of a mixture of air pollutants at the residence, with finer spatial and temporal resolution than in most existing studies, which may explain our ability to detect associations. Chen et al. (2013) who used satellite-based model (2001–2006) and Coogan et al. (2012) who used kriging model based on measurements in year 2000, had estimates of $PM_{2.5}$ levels at the zip-code level (10 km × 10 km). Puett et al. (2011) used GIS-based temporal spatial models for $PM_{2.5}$ estimated at the mix of residential and work (for those missing home addresses) addresses. Park et al. used the hierarchical spatiotemporal model at the address level for $PM_{2.5}$ for the single year (2000) while Weinmayr et al. (2015) used the European Air Pollution Dispersion and Chemistry Transport Model to estimate the $PM_{2.5}$ levels in (mean of 2001 and 2002) at 1 km^2 grid cells.

Our study is directly comparable to Andersen et al. (2012) who in 51,818 subjects from Diet, Cancer, and Health cohort, recruited from two largest Danish cities, detected association between long-term exposure to NO_2 and the incidence of diabetes, with identical definition of diabetes and NO2 as in this study (1.04; 1.01–1.07 per 5.6 μg/m^3), but without PM data. Andersen et al. (2012) detected stronger effects in women (1.07; 1.01–1.13) remarkably comparable to our (1.05; 0.99–1.12 per 7.5 μg/m^3). NO_2 levels were higher in Andersen et al. (2012), comprising of mainly urban population (15.4 μg/m^3) as compared to ours (12.5 μg/m^3) comprising of nurses living mainly in rural and provincial area.

Our finding suggesting that $PM_{2.5}$ is the most relevant pollutant for the development of diabetes is novel. While Chen et al. (2013) had data on $PM_{2.5}$ only, Park et al. (2015) and Coogan et al. (2012) detected stronger associations with NO_x than with $PM_{2.5}$, opposite to our findings. Also in contrast to our findings, Puett et al. (2011) and Weinmayr et al. (2015) both reported stronger associations with coarse particles ($PM_{2.5-10}$) or PM_{10}, respectively, than with $PM_{2.5}$, although only Puett et al. presented two-pollutant models. However, our results agree with experimental studies, in which both short- and long-term exposure to $PM_{2.5}$ among mice provoked visceral adipose inflammation and insulin resistance (Sun et al., 2009), oxidative stress in brown adipose tissue (Xu et al., 2011), and cell stress response and macrophage activation (Mendez et al., 2013), which are all pathophysiological effects of $PM_{2.5}$ on the development of metabolic disorders and diabetes. Furthermore, $PM_{2.5}$ is considered to be the most relevant pollutant for cardiovascular disease (Newby et al., 2015) and overall mortality (Beelen et al., 2014), and given similarity in mechanism involved in cardiovascular disease and diabetes (systemic inflammation, oxidative stress), it is plausible that $PM_{2.5}$ is the most relevant pollutant for development of diabetes.

Our finding of $PM_{2.5}$ for diabetes suggests relevance of secondary pollutants from long-range transport. Gaseous pollution (NO_x and NO_2) is closely linked to traffic emissions in the urban environment (Ellermann et al., 2015). In streets with heavy traffic, up to 90% of the NO_x pollution results from local emissions in the urban environment. In urban background, a little more than half of the NO_x pollution is usually related to sources inside the urban environment, with traffic by far the dominating pollution source in Danish urban environments (Ellermann et al., 2015). The situation is somewhat different with $PM_{2.5}$ where long-range transport plays a dominant role for the levels in Denmark. In urban backgrounds, more than 80% of the $PM_{2.5}$ pollution is the result of long-range transport and in streets with heavy traffic, this contribution is about two thirds of the pollution level. In Brandt et al. (2013) a source allocation for $PM_{2.5}$ for Denmark have been made, showing that around 80% of the total $PM_{2.5}$ mass is coming from abroad and only around 20% are due to sources in Denmark. Dominant sources in Europe are the major coal fired power plants, traffic and farming, while the dominant sources within Denmark are domestic heating (biomass burning), road traffic and farming. The contribution to the chemical composition of $PM_{2.5}$ varies largely with emission sector. Wood burning and coal fired power plants is dominating the contribution to primary particles, especially black carbon and mineral dust, while combustion of fossil fuels in the transport sector and power plants contribute to emissions of nitrogen-oxides, shipping and power plants contributes to emissions of sulfur-oxides and faming dominates the contribution of ammonia emissions. These three species chemically transforms in the atmosphere to secondary inorganic aerosols (SIA), which constitutes a large part of the $PM_{2.5}$. Natural sources like sea salt is important in the coastal areas, but contribute mostly to the coarse particle fraction (PM_{10}). For PM_{10} the local contribution is somewhat larger than for $PM_{2.5}$ due to the relatively fast dry deposition of PM_{10} compared with $PM_{2.5}$. However, our finding that $PM_{2.5}$ may be the most relevant pollutant should be taken with caution, as $PM_{2.5}$ may be

a proxy for other pollutants (such as persistent organic pollutants), other particle size fraction, such as ultrafine particles, or some specific component of $PM_{2.5}$.

It is not clear from existing evidence whether men or women may be more susceptible to effects of air pollution with respect to diabetes. While failing to detect associations in the total population, Brook et al. (2008) and Park et al. (2015) have detected borderline significant association with diabetes prevalence and incidence, respectively, in women, consistent with Chen et al. (2013) and Andersen et al. (2012) who detected stronger association of diabetes incidence with $PM_{2.5}$ and NO_2, respectively, in women. On the contrary, Eze et al. (2014) and Puett et al. (2011) reported stronger associations in men with diabetes prevalence and incidence, respectively, although Puett et al. (2011) did not detect any statistically significant associations. Gender-related differences in susceptibility to air pollution could be associated with physiological differences in inflammatory responses or with differences in exposure due to different activity patterns and life-style. Brook et al. (2008) documented that women spent more time at the home and work closer to home in Canada, contributing to smaller exposure misclassification and stronger air pollution effects, while we do not have data to confirm this pattern in Denmark.

The association between $PM_{2.5}$ and diabetes incidence in this study was limited to current non-smokers (Table 3), in agreement with Andersen et al. (2012) and Weinmayr et al. (2015). Smoking is a risk factor for type 2 diabetes, and tobacco smoke inhalation triggers similar responses as inhalation of $PM_{2.5}$, and the two related exposures share plausible biological mechanism leading to glucose intolerance via oxidative stress and inflammation in adipose tissue. It is thus plausible that current smokers do not have added risk of diabetes related to air pollution exposure. Our results of strongly augmented effects of exposure to $PM_{2.5}$ in nurses with MI (Table 3) corroborates existing evidence suggesting that persons with pre-existing cardiovascular disease are more susceptible to the adverse effects of air pollution (Goldberg et al., 2006). We found indication that obese nurses had higher risk of developing diabetes related to $PM_{2.5}$ than non-obese nurses, in agreement with Andersen et al. (2012), as well as with experimental data which illustrated that obese mice exposed to $PM_{2.5}$ are more likely to develop insulin resistance (Sun et al., 2009). It has been suggested that air pollution can promote weight gain and obesity formation (Jerrett et al., 2014), via systemic inflammation as a key mechanism. Similarly, systemic inflammation in adipose tissue is a key mechanism behind effects of air pollution in promoting development of insulin resistance and diabetes. Thus, it seems plausible that the effect of air pollution is statistically significantly enhanced in obese subjects, with preexisting systemic inflammation, as compared to subjects with normal weight, as observed in our study, and earlier in Andersen et al. (2012) and Weinmayr et al. (2015). However, Chen et al. found higher associations of $PM_{2.5}$ with diabetes in subjects with normal weight than in obese and overweight subjects, although without significant interaction (Chen et al., 2013).

Strengths of this study include the large prospective cohort with an objective assessment of diabetes incidence, well-defined information on diabetes risk factors with minimal possibility of recall and information bias, and state-of-the-art high-resolution exposure model with data on multiple pollutants. This is the first data on the effect of exposure to $PM_{2.5}$ and PM_{10} on diabetes in Denmark. Moreover the AirGIS modeling system has been substantially improved compared to previous applications (Andersen et al., 2012) especially in the way the background pollution is modeled now in more detail. The main limitation is the exposure misclassification in modeled concentrations since these are only proxies of personal exposure, and the lack of information on indoor exposures (gas cooking, passive tobacco smoke, air conditioning, ventilation habits, etc.), air pollution at work, commuting habits and personal activity patterns. However, the air pollution models used to assess levels have been successfully validated (World Health Organization, 2015; Kakosimos et al., 2010), including earlier study on diabetes by Andersen et al. (2012). We had data on lifestyle factors only at the baseline for this cohort, from self-reported questionnaire, and questions on nutrition were vague and limited, precluding more complete adjustment for lifestyle. We lacked data on noise exposure in this cohort. We could not distinguish type 1 diabetes from type 2 diabetes, however, since we studied incidence of diabetes above age 44, majority of cases in this age group are expected to have type 2 diabetes. Diabetes incidence is based on objectively collected data from nationwide health registries with high validity and full coverage on hospitalizations for diabetes, purchase of insulin or oral anti-diabetic medicine, chiropody, or blood-glucose measurements. The NDR register and specifically definition of diabetes used in this study, with exclusion of diabetes cases which are solely based on blood-glucose measurements, has been recently recommended and shown to have high validity (Green et al., 2014). Furthermore, diabetes incidence of 3 new cases per 1000 person-years in female Danish nurses observed in this study was somewhat lower than that observed in women from earlier Danish study by Andersen et al. of 4.4 per 1000 (Andersen et al., 2012), which is likely explained by lower mean age at baseline (54 years) and lower BMI (23.6 kg/m^2) of the nurses than of women from Andersen et al., who were 56 year at baseline (1993–97) and had mean BMI of 26 kg/m^2. Nurses have been found to have in general a healthier lifestyle than a representative sample of Danish women, as they smoked less and had higher physical activity levels, although they consumed more alcohol (Hundrup et al., 2012). Furthermore, there were no major health differences between nurses and Danish women in general with respect to use of health care, disease occurrence, (Hundrup et al., 2012), diabetes prevalence (Carstensen et al., 2008), and it was thus evaluated that it is possible to generalize findings based on this cohort to a general female population. In our cohort prevalence of diabetes at cohort baseline between 1993 and 1999 was 2.5%, which is directly comparable to estimates for entire Danish population of around 2% for this age group, and this time (Carstensen et al., 2008).

In conclusion, in this study in women above age 44, we find that long-term exposure to air pollution increases risk of diabetes, and that fine particles may be most relevant. Non-smokers, obese subjects and cardiovascular disease patients may be most susceptible to development of diabetes related to air pollution. The decrease in air pollution in Denmark is consistent with a tendency seen in the rest of Western Europe (Goldberg et al., 2006) and USA. Our study thus shows that despite improvements in air quality, there are still health risks related to exposure to current levels, arguing for even stricter regulation.

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Duality of interest

None.

Contribution statement

ABH drafted the manuscript. LR performed statistical analyses and contributed to the manuscript preparation. ZJA contributed to the concept and design for the study, secured funding, prepared data for analyses, and supervised LA and ABH in statistical analyses and manuscript preparation, respectively. SL helped secure the funding and contributed with the manuscript preparation. KKA helped with the statistical analyses and supervising of LR. RB created the GIS maps and urbanization variables for the cohort. EB and CY helped drafting the manuscript for important intellectual contents. MK, TB, JB, and OH contributed with

air pollution exposure data, critical interpretation of data, and drafting the manuscript.

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Appendix A. Supplementary data

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